

also have been shown to be useful in assessing tissue perfusion. More invasive techniques, such as mixed venous oxygen saturation, gastric tonometry, and sublingual capnometry, have been investigated but have not proved useful in clinical management. We believe that the clinical assessment, urine output (goal, >20 to 30 mL/hr), and serial lactic acid levels are the best indicators of effectiveness of therapy. Lactic acid levels should decrease within 24 hours if therapy is effective, although normal values may not be reached for several days.

Intravenous access and monitoring

Close monitoring of hemodynamic parameters is central to therapy in patients with **septic shock**. Intravenous access is most rapidly obtained through peripheral sites, ideally with two 16- to 18-gauge catheters. More stable access can be achieved later with central intravenous access, especially if vasopressors are required. Placement of a large-bore introducer catheter in the right internal jugular or left subclavian vein is especially advantageous because it allows the most rapid rate of infusion (6) and provides easy access for placing a pulmonary artery catheter if needed.

Arterial lines should be placed in all patients with **septic shock**. They allow for more reliable monitoring of blood pressure and provide stable access for monitoring blood gases and other laboratory values. The most common sites are the radial, brachial, and femoral arteries. In general, we prefer the femoral site because it is easiest to access; also, central blood pressure is more reliable in patients with **septic shock**.

Pulmonary artery catheters are able to provide important data, such as cardiac output, systemic vascular resistance, pulmonary artery wedge pressure, and mixed venous oxygen saturation. In some cases, these data are useful in determining the origin of the **shock** state and providing rapid assessment of response to various therapies. Although the use of pulmonary artery catheters remains controversial, we believe that potential indications in **septic shock** include the persistent need for moderate or high doses of vasoconstrictors (eg, norepinephrine [Levophed], >10 micrograms/min) despite adequate fluid resuscitation, severe respiratory failure, and the presence of known heart disease and progressive renal insufficiency. Rigorous adherence to standards for data collection and a thorough understanding of hemodynamic physiology are central to the optimal use of pulmonary artery catheters.

Fluids

A number of human and animal studies (7-10) have shown that aggressive volume resuscitation is one of the centerpieces in treatment of **septic shock**. An initial bolus of fluid is appropriate in any **shock** state. The goal of fluid therapy is rapid volume expansion, which results in increased cardiac output and oxygen delivery. Because of the vasodilatation and capillary leak that occur in **septic shock**, most patients require 1 to 2 L of colloid or 4 to 8 L of crystalloid to adequately restore circulating volume (8). In general, we prefer to administer this fluid as a bolus, rather

than a continuous infusion, because this allows more rapid restoration of circulating volume and minimizes the duration of inadequate organ perfusion. Typically, our goal is to increase mean arterial pressure to 65 to 75 mm Hg and improve organ perfusion within 1 hour of the onset of hypotension. While these maneuvers may improve hemodynamics initially, patients often continue to require large volumes of fluid in the 24 to 72 hours after the initial phase.

Physicians have debated about whether fluid should be administered in the form of crystalloid, colloid, or blood products. Crystalloid has the advantages of being relatively inexpensive and readily available. However, 1 L of crystalloid expands plasma volume by only about 200 to 250 mL and may predispose to pulmonary edema. Theoretically, colloids such as albumin and hydroxyethyl starch (Hespan) have the advantage of remaining longer in the intravascular space. Infusion of 1 L of 5% albumin typically expands plasma volume by 500 to 1,000 mL and equilibrates with the interstitium over 7 to 10 days (11). Infusion of 1 L of hydroxyethyl starch typically expands volume by 700 to 1,000 mL, with perhaps 40% of the peak effect persisting for 24 hours (11). Blood products have the advantage of remaining almost wholly intravascular; however, their availability is limited, and they carry a small risk of disease transmission and transfusion reaction.

The type of fluid used probably has **no** significant clinical impact on outcome as long as appropriate clinical end points are used. We generally use repeated boluses of crystalloid (isotonic sodium chloride solution or lactated Ringer's injection), 500 to 1,000 mL intravenously over 5 to 10 minutes, until mean arterial pressure and tissue perfusion are adequate (about 4 to 8 L total over 24 hours for the typical patient). Boluses of 250 mL might be appropriate for patients who are elderly or who have heart disease or suspected pulmonary edema. Because colloids are likely to stay in the vascular space longer, they may have a role when pulmonary edema is a concern. Red blood cells should be reserved for patients with a hemoglobin value of less than 10 g/dL (100 g/L) and either evidence of decreased oxygen delivery or significant risk from anemia (eg, coronary artery disease). Maintaining hemoglobin levels at greater than 8 to 10 g/dL (80 to 100 g/L) has not been shown to be beneficial in other patients (12).

The main complication of fluid resuscitation is tissue edema. Pulmonary edema is the most serious and is commonly manifested by tachypnea, hypoxemia, or decreased pulmonary compliance. Soft-tissue edema typically does not cause a problem, with the exception of a possible increased risk of skin breakdown. The occurrence of these problems is chiefly related to reduced microvascular permeability, increased hydrostatic pressure, and decreased colloid oncotic pressure.

Vasoactive agents

Patients who do not respond to fluid therapy should receive vasoactive agents. Physicians have debated about which

vasoactive agents are best in **septic shock**. The primary goal is to rapidly normalize tissue perfusion pressure by increasing mean arterial pressure to 65 to 75 mm Hg. Increases in myocardial contractility, when appropriate, and improved oxygen delivery to tissues also are desirable.

Agents most commonly used are dopamine hydrochloride (Intropin), norepinephrine, dobutamine (Dobutrex), epinephrine, and phenylephrine hydrochloride (Neo-Synephrine). The receptor activities, hemodynamic effects, and typical dosing regimens of these agents are shown in tables 1 and 2. The doses listed are those typically used in clinical practice, but they may vary greatly in individual patients. Dopamine traditionally has been used as the initial therapy in hypotension, primarily because it is thought to increase systemic blood pressure through both improved cardiac performance and increased systemic vascular resistance. However, dopamine is a relatively weak vasoconstrictor in **septic shock**. Additionally, we do not recommend the use of low-dose dopamine, because a recent randomized placebo-controlled trial (13) failed to demonstrate its efficacy in improving renal function.

Table 1. Receptor activity of vasoactive agents

| Agent | Activity at receptors | | | |
|---------------------------------------|------------------------------|--------------|--------------|---------------------|
| | alpha1 | beta1 | beta2 | Dopaminergic |
| Dopamine HCl (Inotropin)* | 2+ | 3+ | 2+ | 3+ |
| Norepinephrine (Levophed) | 3+ | 2+ | ? | 0 |
| Dobutamine (Dobutrex) | 1/2+ | 3+ | 2+ | 0 |
| Epinephrine* | 2/3+ | 3+ | 3+ | 0 |
| Phenylephrine HCl (Neo-Synephrine) | 3+ | 0 | 0 | 0 |

Ratings indicate degree of activity from none (0) to maximal (3+).

*Activity is dose-dependent.

Table 2. Hemodynamic effects of vasoactive agents

| Agent | Dose | Effect |
|--------------|-------------|---------------|
|--------------|-------------|---------------|

| | | | CO | MAP | SVR |
|---------------------------------------|-----------------------------|-----------|-----------|-----|-----|
| Dopamine HCl (Inotropin)* | 5-20 micrograms/kg/min | 2+ | 1+ | 1+ | |
| Norepinephrine (Levophed) | 0.05-5 micrograms/kg/min | - /0/+ | 2+ | 2+ | |
| Dobutamine (Dobutrex) | 5-20 micrograms/kg/min | 2+ | - /0/+ | - | |
| Epinephrine* | 0.05-2 micrograms/kg/min | 2+ | 2+ | 2+ | |
| Phenylephrine HCl (Neo-Synephrine) | 2-10 micrograms/kg/min | -/0 | 2+ | 2+ | |

Ratings indicate degree of effect from modest decrease (-) to marked increase (2+). CO, cardiac output; MAP, mean arterial pressure; SVR, systemic vascular resistance.

*Activity is dose-dependent.

Many patients have persistently low blood pressure when receiving dopamine therapy. Evidence suggests that norepinephrine is superior to dopamine in the treatment of hypotension associated with **septic shock**. Martin and colleagues (14) studied 32 patients with **septic shock** unresponsive to fluids. They randomly assigned patients to receive a 6-hour infusion of either dopamine or norepinephrine. Fifteen of 16 patients in the norepinephrine group had improved hemodynamics compared with 5 of 16 in the dopamine group. Patients who received norepinephrine had higher urine output and more improvement in lactic acid levels than patients who received dopamine. Several other studies have shown improved splanchnic tissue perfusion with norepinephrine compared with dopamine.

Like norepinephrine, epinephrine and phenylephrine are more potent vasoconstrictors than dopamine. Few clinical studies have compared these agents, but limited data thus far suggest that norepinephrine is the agent of choice for treatment of hypotension related to **septic shock**. Dobutamine should be reserved for patients with a persistently low cardiac index or underlying left ventricular dysfunction. In general, we do not set an upper limit on such agents as norepinephrine or phenylephrine, but it is our experience that patients who require more than 200 micrograms/min of norepinephrine for longer than 24 hours rarely survive.

Vasopressin (Pitressin) also has been evaluated in a few studies to assess its pressor effect in **septic shock**. It has little pressor effect in healthy persons, but it has been shown to increase blood pressure in patients with sepsis (15,16). This may occur through improvement of sympathetic function, which has been shown to be abnormal in sepsis. Patients with **septic shock** have been shown to have low circulating levels of vasopressin. The data to this point are too limited to make firm recommendations, but further study is warranted.

Antibiotics

Antibiotics remain one of the few therapies that have been shown to reduce mortality rates in **septic shock**. They should be administered within 2 hours of the recognition of sepsis. The agent chosen depends largely on the host status and suspected causative organism. Important factors to consider include the suspected source of infection, nature of the pathogen most likely responsible (community or nosocomial), local resistance patterns, and underlying immune status of the patient. Sicker patients require broader coverage. For any given pathogen or source, numerous regimens are likely to be effective (table 3).

Table 3. Recommended antibiotics in septic shock

| Suspected source | Recommended antibiotics |
|-------------------------|---|
| Pneumonia | Second- or third-generation cephalosporin <i>plus</i> macrolide (antipseudomonal beta lactam <i>plus</i> aminoglycoside if hospital-acquired) |
| Urinary tract | Ampicillin <i>plus</i> gentamicin (Garamycin) or third-generation cephalosporin |
| Skin or soft tissue | Nafcillin sodium (Nafcil, Nallpen, Unipen) (add metronidazole [Flagyl, Metro IV, Protostat] or clindamycin if anaerobic infection suspected) |
| Meningitis | Third-generation cephalosporin |
| Intra-abdominal | Third-generation cephalosporin <i>plus</i> metronidazole or clindamycin |
| Primary bacteremia | Ticarcillin and clavulanate potassium (Timentin) <i>or</i> piperacillin sodium and tazobactam sodium (Zosyn) |

The overuse of vancomycin hydrochloride (Vancocin,

Vancoled) and its contribution to the development of multidrug-resistant pathogens are of great concern. Use of vancomycin should be restricted to settings in which the causative agent is most likely resistant *Enterococcus*, methicillin-resistant *Staphylococcus aureus*, or high-level penicillin-resistant *Streptococcus pneumoniae*.

Oxygen balance

Lactic acidosis, a hallmark of **septic shock**, is a result of an imbalance between oxygen delivery and consumption. Potential causes of this imbalance include inadequate oxygen delivery, increased oxygen consumption, and an inability of tissues to optimally use oxygen. Oxygen delivery to the tissues can be optimized by maintaining arterial oxygen saturation at more than 90% and hemoglobin at more than 8 g/dL (80 g/L) and by increasing the cardiac index to between 4.5 and 6 L/min per square meter of body surface area. The latter can be accomplished by the use of fluids to maintain adequate pulmonary artery wedge pressure (10 to 14 mm Hg) and through use of such positive inotropic agents as dobutamine. These interventions are often best achieved with the aid of a pulmonary artery catheter.

Initial investigation suggested that routinely maintaining supranormal oxygen delivery improves outcome, especially in high-risk surgical patients (17). However, these results have not been duplicated in most studies of **septic shock**, and therefore this approach is not recommended. While lactic acidosis most commonly represents poor tissue perfusion, experimental models also have demonstrated abnormal oxidative metabolism by peripheral tissues despite normal perfusion pressure and oxygen delivery (18,19).

Oxygen balance in **septic shock** also can be improved by reducing oxygen consumption. Control of fever can reduce oxygen consumption by about 20% (20). If the work of breathing is substantial, intubation and mechanical ventilation, along with sedation and neuromuscular blockade, can have similar effects (21).

Other therapies

Even with aggressive treatment of **septic shock**, a substantial number of patients remain hypotensive or demonstrate significant tissue hypoperfusion, or both. Several other therapies are used in refractory **septic shock**.

Use of corticosteroids in the treatment of **septic shock** has been controversial. Numerous studies in the 1980s and early 1990s generally showed **no** significant improvement with corticosteroid therapy, and some even showed increased morbidity (22). More recently, investigations have focused on use of more modest doses of corticosteroid in patients with refractory **shock** despite adequate resuscitation. A recent randomized placebo-controlled study of hydrocortisone (100 mg every 8 hours) in 41 patients with refractory **shock** (23) showed a significant improvement in hemodynamics and a trend toward improved survival rates regardless of the results of a corticotropin stimulation test. The data in this area are limited, but these and other results

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Therapy for septic shock

Bacterial sepsis remains a major challenge for modern medicine. **Septic shock** is the most severe form of sepsis, in which perfusion of the liver, kidney and other vital organs is compromised. This syndrome, which can be caused by both gram-negative and gram-positive bacteria, has a mortality rate of 30-60%. Systemic infection is a complication of many types of medical therapy, such as surgery, immuno-suppression for transplant or cancer chemotherapy. There are **currently no effective treatments** for sepsis and the number of patients in the US and Europe is large and will likely increase as intensive medical therapy becomes more widespread.

The lipopolysaccharide (LPS) from gram-negative bacterial cell walls is the most well established trigger of **septic shock**. Mutant versions of a naturally occurring protein have recently been shown to inhibit the induction of inflammatory cytokines by LPS in cell culture. Administration of these molecules has the potential to prevent or ameliorate the induction of **septic shock in vivo**. These mutant proteins could also be further modified to improve their therapeutic capabilities and they provide a promising new approach to the treatment of **septic shock**.

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endotoxic shock in mice. The mechanisms of the anti-inflammatory effect of MG is, at least in part, dependent on the inhibition of NO formation.

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suggest that corticosteroids may be beneficial in a subset of patients with refractory **shock**.

Infusions of sodium bicarbonate long have been advocated to correct persistent metabolic acidosis. The argument is made that infusion of sodium bicarbonate results in increased pH with less cellular dysfunction, improved cardiac contractility, and improved activity of vasopressor agents. It also is argued that there is little detrimental effect and that this therapy should be tried as a last resort to improve the patient's clinical status. In a recent review (24), the data supporting sodium bicarbonate infusion were evaluated. It seems clear from animal data that artificially increasing the pH does not improve such parameters as cardiac function, although this is difficult to measure in humans. Furthermore, it is not clear that raising the serum pH has any effect on pH at a local tissue or intracellular level. Finally, sodium bicarbonate is converted to carbon dioxide and water, resulting in increased carbon dioxide levels and possible further depression of pH. We do not advocate the routine use of sodium bicarbonate in lactic acidosis.

Nitric oxide, which is released from endothelial cells, probably contributes to vasodilatation and perhaps to cardiac depression. Inhibition of nitric oxide synthesis by methylene blue (Methblue 65, Urolene Blue) has been shown to improve mean arterial pressure in patients with **septic shock** (25,26) but may have deleterious effects; data are limited. Naloxone hydrochloride (Narcan), an opioid antagonist, may block the endorphin effect that occurs in sepsis and improve hemodynamics in patients with **septic shock** (27,28). A recent meta-analysis (29) of three randomized controlled clinical trials of this agent showed modest hemodynamic improvement but **no** clear improvement in mortality rates. Further investigation probably is warranted before either of these therapies is universally adopted.

A host of multicenter randomized trials have evaluated inhibition of various cytokines thought to participate in the sepsis cascade. Monoclonal antibody to endotoxin, antibody to IL-1 receptor, antibradykinin, antiplatelet activating factor, anti-tumor necrosis factor, and nonsteroidal anti-inflammatory drugs have been studied. Improvement in mortality rates in sepsis or **septic shock** has not been demonstrated with any of these agents. This likely reflects the complexity of interactions between exogenous factors and the inflammatory and anti-inflammatory cascades.

An exciting recent finding has been the role of activated protein C in the treatment of **septic shock**. This compound has antithrombotic, profibrinolytic, and anti-inflammatory properties. A recent multicenter randomized placebo-controlled trial of more than 1,600 patients (30) showed that patients with **septic shock** who underwent treatment with activated protein C had a relative reduction in risk of death of 20%. The treated group had a small but statistically significant risk of bleeding. This winter, activated protein C (drotrecogin alfa) (Xigris) received approval from the US Food and Drug Administration for treatment in patients with

severe sepsis who are at high risk of death. We recommend consideration of drotrecogin alfa mainly in patients with an APACHE II score greater than or equal to 25 or with significant organ dysfunction (especially refractory dysfunction or multiorgan dysfunction). Ultimately, the potential risks and benefits of this agent must be carefully weighed in each patient. Drotrecogin alfa is administered as a 96-hour infusion at a cost of about \$6,800 for treatment in a 154-lb patient.

Summary

Septic shock is a common problem in hospitalized patients. Optimal management depends on rapid recognition, aggressive restoration of circulating volume with fluid boluses, initiation of appropriate antibiotic therapy, implementation of adequate monitoring, and meticulous attention to the details of care. Mean arterial pressure should be increased to between 65 and 75 mm Hg as soon as possible to reduce the likelihood of multiorgan dysfunction. Despite these therapeutic maneuvers, however, mortality rates are likely to remain high until the development of therapies that better target the underlying mechanisms of sepsis.

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Effect of methylguanidine in a model of septic shock induced by LPS.

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Septic shock, a severe form of sepsis, is characterized by cardiovascular collapse following microbial invasion of the body. The progressive hypotension, hyporeactivity to vasopressor agents and vascular leak leads to circulatory failure with multiple organ dysfunction and death. Many inflammatory mediators (e.g. TNF-alpha, IL-1 and IL-6) are involved in the pathogenesis of shock and, among them, nitric oxide (NO). The overproduction of NO during septic shock has been demonstrated to contribute to circulatory failure, myocardial dysfunction, organ injury and multiple organ failure. We have previously demonstrated with *in vitro* and *in vivo* studies that methylguanidine (MG), a guanidine compound deriving from protein catabolism, significantly inhibits iNOS activity, TNF-alpha release and carrageenan-induced acute inflammation in rats. The aim of the present study was to evaluate the possible anti-inflammatory activity of MG in a model of septic shock induced by lipopolysaccharide (LPS) in mice. MG was administered intraperitoneally (i.p.) at the dose of 30 mg/kg 1 h before and at 1 and 6 h after LPS-induced shock. LPS injection (10 mg/kg in 0.9% NaCl; 0.1 ml/mouse; i.p.) in mouse developed a shock syndrome with enhanced NO release and liver, kidney and pancreatic damage 18 h later. NOx levels, evaluated as nitrite/nitrate serum levels, was significantly reduced in MG-treated rats (78.6%, $p < 0.0001$; $n = 10$).

Immunohistochemistry revealed, in the lung tissue of LPS-treated group, a positive staining for nitrotyrosine and poly(adenosine diphosphate [ADP] ribose) synthase, both of which were reduced in MG-treated mice.

Furthermore, enzymatic evaluation revealed a significant reduction in liver, renal and pancreatic tissue damage and MG treatment also improved significantly the survival rate. This study provides evidence that MG attenuates the degree of inflammation and tissue damage associated with

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Current Issues in Hypertension

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Opinion statement The optimal therapy for the treatment of sepsis and septic shock remains controversial. Many protocols are followed, using different strategies for initial resuscitation, cardiovascular monitoring, hemodynamic intervention, and eradication of infection. Overall, an aggressive approach to the management of cardiovascular dysfunction in septic shock is warranted. Initially, large volume fluid resuscitation is instituted. Our first choice of resuscitation fluid is 0.9% normal saline. Invasive hemodynamic monitoring using a flotation pulmonary artery catheter as well as invasive arterial blood pressure monitoring is a necessity in the hemodynamic management of septic shock. If the patient remains hypotensive (mean arterial pressure < 65 mm Hg) after adequate volume resuscitation has been established (pulmonary capillary wedge pressure 12 to 15 mm Hg), then vasopressor agents must be instituted. Our first choice is usually dopamine. In patients who remain hypotensive after maximal doses of dopamine are reached, norepinephrine is added. If these agents generate excessive tachycardia or if tachyarrhythmias develop, phenylephrine can be substituted or added. Inotropic agents are useful if the patient demonstrates hypotension with a low cardiac output state. Dobutamine is the agent of choice. We initiate broad-spectrum empiric antibiotics at presentation, modifying the exact regimen based on 1) site of infection; 2) prevailing organisms and antibiotic resistance

patterns in the patient's environment; and 3) other specific risk factors (immunosuppression, chronic disease, exposure and vaccination history, invasive medical devices). When appropriate, aggressive surgical debridement is pursued. Currently, there are no clinical data to support the use of antagonists for sepsis mediators, although various clinical trials remain underway. Steroids are contraindicated except for adrenal replacement therapy.

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